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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Clark, et al.

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Group Art Unit: 1646

#6
D.J.
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FOR: METHODS FOR DIAGNOSING GLAUCOMA AND DISCOVERING ANTI-GLAUCOMA DRUGS

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, ABBOT F. CLARK, hereby say and declare as follows:

1. I received my bachelor's degree in biology from Thiel College in Greenville, Pennsylvania (1973) and my doctor of philosophy in microbiology from Case Western Reserve University in Cleveland, Ohio (1981). I began working at Alcon Laboratories, Inc. in 1985 where I have worked in research including the study of normal and diseased eye tissues and the identification of pharmaceuticals useful in treating ocular diseases, such as, autoimmune disorders and glaucoma. In particular, I have worked and published extensively on the cellular and molecular biology of glaucoma and the relationship between glucocorticoids and glaucoma.

2. I am familiar with the present specification and the claims.

3. The human glucocorticoid receptor (GR) gene has been well defined and characterized (Hollenberg et al., Nature, Vol. 318:635-641, 1985; Giguère et al., Cell, Vol. 46:645-652, 1986; Encio, et al., Journal of Biological Chemistry, Vol. 266(11):7182-7188, 1991). The gene products of the GR gene consist of 2 alternatively spliced variants GRα and GRβ, each of which is well characterized (Hollenberg *supra*; Giguère *supra*; Encio *supra*). The nucleotide sequences for these gene products can be found in the NCBI gene database (assession # M10901 for GRα and assession # X03348 for GRβ), and the normal alternative splicing scheme for GRα and GRβ has been reported (Encio *supra*; Oakley, et al., Journal of

Biological Chemistry, Vol. 271(16):9550-9559, 1996; Oakley et al., Endocrinology, Vol. 138(11):5028-5038, 1997; Wordinger, et al., Progress in Retinal and Eye Research, Vol. 18(5):6629-667, 1999). An "aberrant alternative slice form of the human glucocorticoid receptor (GRβ)" is defined as any different oligonucleotide sequence for GRβ that is due to a different post-transcriptional splicing event(s) compared to what has been documented in the above references.

4. The term "genetic changes" is well known by those skilled in the art. There are numerous examples of diseases associated with genetic changes in specific genes (for examples see Cummings, Michael R., Human Heredity, Fourth Edition, 1997; Strachan, et al., Human Molecular Genetics, 1996; Jorde, et al., Medical Genetics, Second Edition, 1999). Genetic changes in a specific gene (e.g. GRβ) can be determined using a variety of techniques well known by those skilled in the art, such as: SSCP, DGGE, ASO, RFLP, heteroduplex analysis, CCM, PTT, and RNase cleavage (see Birren, et al., Genome Analysis, Vol. 2, 1998).

5. "Altered GRβ gene expression" means expression of this gene product that is different from normal. The normal GRβ gene has been well characterized (see above), and the expression of GRβ has been reported in a variety of tissues (Hollenberg *supra*; Giguère *supra*; Bamberger, et al., Journal of Clinical Investigation, Inc., Vol. 95:2435-2441, June 1995; Leung, et al., Journal of Experimental Medicine, Vol. 186(9):1567-1574, November 3, 1997; Oakley, 1996, *supra*; Oakley, 1997, *supra*). We have found that GRβ expression in the trabecular meshwork, a tissue involved in glaucoma pathogenesis, is different (i.e. altered) in glaucoma patients compared to age matched non-glaucomatous individuals.

6. It is well known by those skilled in the art that "changes outside" of the coding region of a specific gene are important in the regulation of gene expression. For example, the region upstream (5') of the coding region of most genes is known as the promoter region which "promotes" and regulates the expression of that gene. The promoter region contains numerous nucleotide sequences recognized by various transcription factors and DNA binding proteins that are responsible for activation or repression of gene expression. Regions downstream (3') of the gene can determine poly-adenylation of the gene product, thereby regulating RNA processing and translation of the gene product.

7. Copies of the references (except the books) cited herein are included with this Declaration.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

April 12, 2001
Date

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